Variations in Outpatient Antimicrobial Use Between and Within Countries: An Ongoing Mystery

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Important progress has been made during the last decade in terms of standardized antibiotic usage studies that allow comparisons between countries. The driving force behind this development has been the European Surveillance of Antimicrobial Consumption (ESAC) project [1, 2]. One of the most striking observations remains the marked international differences in the volume and pattern of outpatient antibiotic use. In the current issue of INFECTION, Nitzan and colleagues [3] report detailed data on outpatient antibiotic use in a country participating in ESAC (Israel) that were collected between 2003 and 2005.

The researchers analyzed prescription data from the largest Health Maintenance Organization in Israel, which covers slightly more than half of the total population. They found a modest, yet significant reduction in outpatient antibiotic use over the study period. This finding should, however, be interpreted with caution. As mentioned by the authors [3], analyzing trends over just a 3-year period is problematic. Most importantly, recent ESAC data for Israel, which presumably come from the same data source, do not confirm the positive trend reported by the authors. The ESAC data for 2006 show an increase in antibiotic use to 22.2 defined daily doses (DDD)/1,000 inhabitants per day [4]. It would thus have been interesting to have seen more recent data included in this study. Moreover, this recently observed opposite trend demonstrates the dangers of overinterpreting temporary trends over short study periods, which may just be the result of random or seasonal variation in the incidence of respiratory tract infections and influenza. Clearly, before drawing any firm conclusions, researchers are well advised to generate more extended time-series and to analyze these with accurate statistical analytical methods that account for the interdependence of data points [5].

Nitzan and colleagues [3] also found differences in the quantity and quality of antibiotic prescribing between different regions within Israel. This observation confirms observations from several other countries [6, 7]. As is the case for variations in antibiotic use between countries, the reasons for variations between regions are only incompletely understood and difficult to pin down, although they certainly involve socio-cultural and demographic factors (including physician density) more than differences in disease incidence and presentation [8, 9]. Interestingly, the researchers from Israel explored the potential association between demographic data and regional variation in antibiotic use. They found that the age distribution within a region influences antibiotic consumption patterns, which is not surprising since antibiotic prescribing for children is particularly high. Moreover, after performing a multivariate analysis, Nitzan and colleagues [3] found a significant association between antibiotic consumption and the prevalence of diabetes mellitus in certain regions. Although this finding may be plausible considering the many chronic health problems of diabetic patients, it should be interpreted with caution, since the use of individual patient data may have given different results. As stated by the authors, the true reasons for the interregional variation in Israel remain elusive.

How should clinicians and policy-makers interpret these findings from Israel? The total volume of outpatient antibiotic use in Israel is similar to that of the USA, Australia, Spain, and Italy and relatively high compared to some Northern or Central European countries [1, 2, 10]. Although Israel has a high density of academic centers with renowned infectious disease services, this does not seem to protect the country against antibiotic misuse by general practitioners and pediatricians, who may be more influenced by patient expectations and beliefs, knowledge gaps, diagnostic uncertainty, and marketing pressure. Some experts even argue that in many countries such as Israel, tight links between academic opinion leaders and the pharmaceutical industry may have accelerated the diffusion and overuse of new broad-spectrum antibiotics both in the inpatient and outpatient settings.

Antibiotic use is associated with the selection and creation of antibiotic resistant bacteria and reducing antibiotic use can positively influence antibiotic resistance [11, 12]. This is nicely illustrated by two recent studies from Israel.

Infection 2010; 38: 1–2
DOI 10.1007/s15010-009-9350-6
Published online: January 27, 2010

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In the first study, Dagan and colleagues [13] showed that the lower antibiotic use in Jewish children during the summer months is associated with lower rates of antibiotic resistance in *Streptococcus pneumoniae* during these months. In a second study, Gottesman and colleagues [14] found that a widespread decrease in fluoroquinolone use after introduction of a short-term national restriction policy in 2001 led to an increase in susceptibility to fluoroquinolones of *Escherichia coli* in urinary isolates, which reversed immediately when fluoroquinolone consumption increased again.

National campaigns in Belgium and France have recently shown that it is possible to reduce outpatient antibiotic use by extended mass media campaigns [6, 15, 16]. Similar campaigns to reduce unnecessary antibiotic use have been conducted in Israel by another HMO [17], different from that described in the article by Nitzan et al. [3]. A recent paper suggests that the 2006 campaign on antibiotic prescribing has had some impact, at least in the HMO organizing the campaign. In Europe, evidence on the best ways to promote judicious outpatient antibiotic use has been gathered in the context of the EU-funded CHAMP project (Changing Behavior of Health Care Professionals and the General Public Towards a More Prudent Use of Anti-Microbial Agents), whose aim is to develop recommendations for policy-makers on how to improve outpatient antibiotic use [18].

Studies such as the one by Nitzan and colleagues [3] are important in order to gain further insight into the reasons for variations in antibiotic use within or between countries. They should, however, be followed by well-designed interventions to reduce unnecessary antibiotic use adapted to the specific country setting. Clearly, there is still room for improvement in Israel (as in many other countries). Although the optimal level and pattern of outpatient antibiotic use are not clear, it is probably safe to assume that it can be reduced to the level of several European countries that are below 15 DDD/1,000 inhabitants per day, without harming patient safety and increasing the risk of major adverse outcomes.

Acknowledgments

This article was supported in part by the 6th Framework Programme of the European Community in the context of the project "Changing Behavior of Health Care Professionals and the General Public Towards a More Prudent Use of Anti-Microbial Agents" (acronym CHAMP, network contract SP5A-CT-2007-044317).

Conflict of interest statement. The authors have declared that no competing interests exist.

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